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# Journal Pre-proof

Clinical Benefit of Lenzilumab in Cases of Coronavirus Disease 2019

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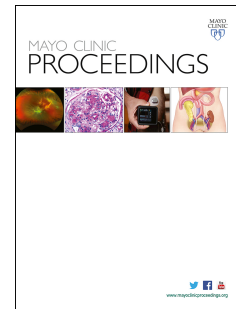
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## **Clinical Benefit of Lenzilumab in Cases of Coronavirus Disease 2019**

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**Letter to the Editor****Clinical Benefit of Lenzilumab in Cases of Coronavirus Disease 2019**

To the Editor: Temesgen et al<sup>1</sup> carefully depicted the clinical benefit provided by Lenzilumab in cases of coronavirus disease 2019 (COVID-19), sustained by the novel severe acute respiratory coronavirus 2 (SARS-CoV-2), where cytokine storm may lead to fatal multi-organ failure. Lymphopenia is a typical finding occurring at early onset of the disease and Lenzilumab administration showed a significant improvement in terms of lymphocyte count, which has not been fully understood by the Authors, suggesting that granulocyte-monocyte colony-stimulating factor (GM-CSF) might have a direct impact on T cells.

SARS-CoV-2 related hyperinflammatory pattern resembles the cytokine release syndrome (CRS) occurring in Chimeric Antigen Receptor (CAR) T cell therapy, where host monocyte-macrophage system is the major source of cytokine production (e.g. interleukin (IL)-1 and IL-6).<sup>2</sup> In this setting, Lenzilumab showed to be effective in reducing CAR T-mediated CRS and neuroinflammation at the same time, enhancing adoptive T cell therapy as well.<sup>3</sup>

Previous preclinical data in SARS-CoV infected mice showed that inflammatory monocyte-macrophage response, secondary to dysregulated type-I interferon activity during SARS-CoV infection, results in lethal pneumonia and cytokine-induced apoptosis of T cells (specifically mediated by tumor necrosis factor alpha – TNF- $\alpha$ ).<sup>4</sup>

As already known, GM-CSF inhibition turned out to broadly modulate monocyte-macrophage activity by simultaneously reducing a spectrum of inflammatory cytokines, including TNF- $\alpha$ .<sup>3</sup> We therefore suggest that the direct regulation of monocyte-macrophage activity by Lenzilumab, with subsequent broad cytokines shutdown, could provide a more favorable micro-environment where effector T cells could also be protected from cytokine-induced apoptosis. This would preserve a non-exhausted T cell phenotype, being more effective against infections and performing more potently T cell specific antiviral immunity to achieve viral clearance.

Aware of the good safety profile of Lenzilumab in this current study and previous analysis,<sup>1,5</sup> the treatment is feasible and safe and the ongoing randomized phase III trial (NCT04351152) will extensively confirm the lymphocyte recovery in Sars-CoV-2 infection and the impact of the drug on COVID-19 clinical improvement.

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